

DOCKET NO.: ISIS-2297
 Application No.: 08/973,381
 Office Action Dated: June 17, 2003

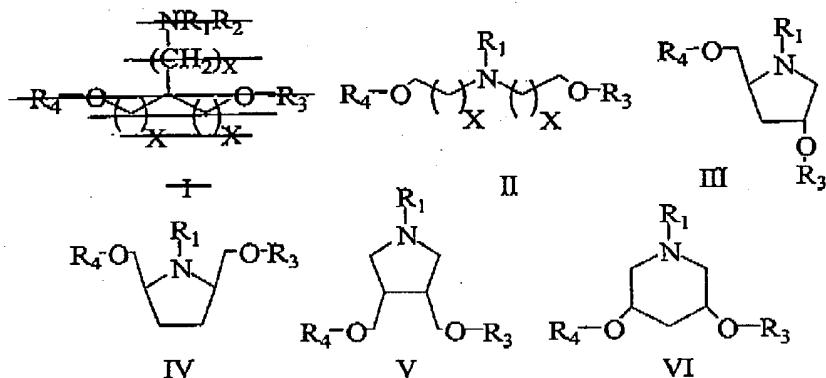
PATENT
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 PROCEDURE PURSUANT TO
 37 CFR § 1.116

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. – 30. (Canceled)

31. (Currently Amended) An oligomeric compound comprising a plurality of aminodiol monomer subunits joined by linking groups, wherein each of said aminodiol monomer subunits has one of the structures I, II, III, IV, V or VI:



wherein:

each x is, independently, 0 to 5;

R₁ is -T-L or a base labile protecting group;

T is a single bond, a methylene group or a group having formula:



wherein:

R₁₀ is =O, =S, or =NR₁₁;

R₅ and E, independently, are a single bond, CH=CH, C≡C, O, S, NR₁₁, or C₆-C₁₄ aryl;

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each R₆, R₇, R₈, R₉, R₁₁, R₁₂ and R₁₃ are, independently, H, alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, or aryl having 7 to about 14 carbon atoms;

m and n, independently, are 0 to 5;

p is 0 or 1;

q is 1 to about 10;

L is H, substituted or unsubstituted C₂-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, substituted or unsubstituted C₄-C₇ carbocyclic alkyl, substituted or unsubstituted C₄-C₇ carbocyclic alkenyl, substituted or unsubstituted C₄-C₇ carbocyclic alkynyl, substituted or unsubstituted C₆-C₁₄ aryl, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, a nitrogen containing heterocycle, a sulfur containing heterocycle, an oxygen containing heterocycle, a metal coordination group, a conjugate group, halogen, hydroxyl (OH), thiol (SH), keto (C=O), carboxyl (COOH), amide (CONR₁₂), amidine (C(=NH)NR₁₂R₁₃), guanidine (NHC(=NH)NR₁₂R₁₃), glutamyl (R₁₂OOCCH(NR₁₂R₁₃)(CH₂)₂C(=O)), nitrate (ONO₂), nitro (NO₂), nitrile (CN), trifluoromethyl (CF₃), trifluoromethoxy (OCF₃), O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aralkyl, S-aralkyl, NH-aralkyl, amino (NH₂), azido (N₃), hydrazino (NNNH₂), hydroxylamino (ONH₂), sulfoxide (SO), sulfone (SO₂), sulfide (S-), disulfide (S-S), silyl, a nucleosidic base, an amino acid side chain, a carbohydrate, a biopharmaceutically active moiety, or group capable of hydrogen bonding where the substituent groups are selected from hydroxyl, amino, alkoxy, alcohol, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, and alkynyl groups;

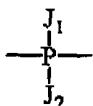
R₂ is hydrogen or C₁-C₁₀ alkyl;

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R_3 and R_4 are independently hydrogen, an acid labile hydroxyl protecting group, a linking group or a conjugate group, wherein said linking group has the formula:



wherein:

J_1 is $=O$ or $=S$;

J_2 is OH or $N(Y_0)T_0$;

Y_0 is H or $(Q_2)_j-Z_2$;

T_0 is $(Q_1)_k-Z_1$, or together Y_0 and T_0 are joined in a nitrogen heterocycle;

Q_1 and Q_2 independently are C_2-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_4-C_7 carbocylo alkyl C_4-C_7 carbocylo alkenyl, a heterocycle, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, a polyalkyl glycol, or C_7-C_{14} aralkyl;

j and k independently are 0 or 1;

Z_1 and Z_2 independently are H , C_1-C_2 alkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_7-C_{15} aralkyl, halogen, $CH=O$, OR_{12} , SR_{12} , $NR_{12}R_{13}$, $C(-NH)NR_{12}R_{13}$, $CH(NR_{12}R_{13})$, $NHC(=NH)NR_{12}R_{13}$, $CH(NH_2)C(=O)OH$, $C(=O)NR_{12}R_{13}$, $C(=O)OR_{12}$, a metal coordination group, a reporter group, a nitrogen-containing heterocycle, a purine, a pyrimidine, a phosphate group, a polyether group, or a polyethylene glycol group; and

provided that at least one of said aminodiol monomer subunits in said oligomeric compound does not have structure III.

32. (Previously Presented) The oligomeric compound of claim 31 wherein said J_1 is $=O$ or $=S$ and said J_2 is OH .

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33. (Previously Presented) The oligomeric compound of claim 31 wherein said J_1 is $=O$, said J_2 is $N(Y_0)T_0$ and at least two of said $N(Y_0)T_0$ are the same.

34. (Previously Presented) The oligomeric compound of claim 31 wherein said J_1 is $=O$, said J_2 is $N(Y_0)T_0$ and wherein at least two of said $N(Y_0)T_0$ are different.

35. (Previously Presented) The oligomeric compound of claim 31 wherein each of said R_1 are the same.

36. (Previously Presented) The oligomeric compound of claim 31 wherein at least two of said R_1 are different.

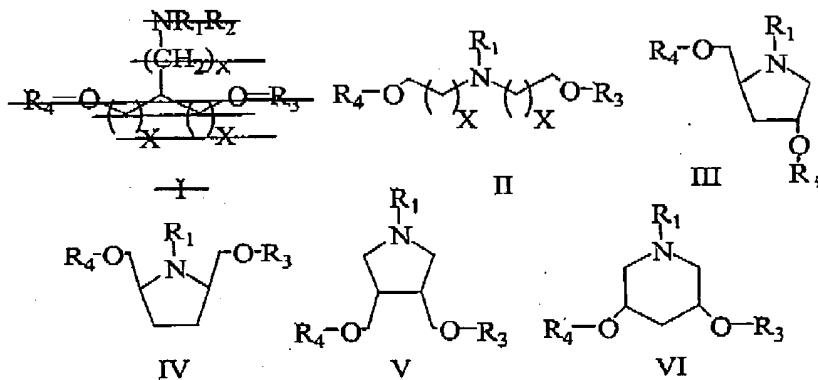
37. (Previously Presented) The oligomeric compound of claim 31 wherein each of said aminodiol monomer subunits are the same.

38. (Previously Presented) The oligomeric compound of claim 31 wherein at least two of said aminodiol monomer subunits are different.

39-44. (Cancelled)

45. (Currently Amended) A method for preparing an oligomer comprising:

(a) selecting an aminodiol monomer subunit having the structure I, II, III, IV, V, or VI:



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wherein:

each x is, independently, 0 to 5;

R₁ is a base labile amino protecting group;

R₂ is hydrogen or C₁-C₁₀ alkyl;

one of R₃ or R₄ is hydrogen or an activated phosphite group and the other of R₃ or R₄ is an acid labile hydroxyl protecting group;

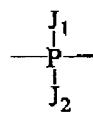
(b) attaching said aminodiol monomer subunit to a solid support to form a solid support bound aminodiol monomer subunit;

(c) treating said acid labile hydroxyl protecting group with a dilute acid to form a free hydroxyl group;

(d) reacting said free hydroxyl group with a further aminodiol monomer subunit having structure I, II, III, IV, V, or VI thereby forming an oligomeric compound bound to said solid support, said oligomeric compound containing a phosphite linkage;

(e) optionally iteratively repeating steps (c) and (d) to increase the length of the oligomeric compound bound to said solid support;

(f) optionally, prior to step (c) or after step (d) oxidizing said phosphite linkage to form a phosphate linking group wherein said linking groups are selected having formula:



wherein:

J₁ is =O or =S;

J₂ is OH or N(Y₀)T₀;

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Y_0 is H or $(Q_2)_j\text{-}Z_2$;

T_0 is $(Q_1)_k\text{-}Z_1$, or together Y_0 and T_0 are joined in a nitrogen heterocycle;

Q_1 and Q_2 independently are $C_2\text{-}C_{10}$ alkyl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $C_4\text{-}C_7$ carbocylo alkyl $C_4\text{-}C_7$ carbocylo alkenyl, a heterocycle, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, a polyalkyl glycol, or $C_7\text{-}C_{14}$ aralkyl;

j and k independently are 0 or 1;

Z_1 and Z_2 independently are H, $C_1\text{-}C_2$ alkyl, $C_2\text{-}C_{20}$ alkenyl, $C_2\text{-}C_{20}$ alkynyl, $C_6\text{-}C_{14}$ aryl, $C_7\text{-}C_{15}$ aralkyl, halogen, $CH=O$, OR_{12} , SR_{12} , $NR_{12}R_{13}$, $C(=NH)NR_{12}R_{13}$, $CH(NR_{12}R_{13})$, $NHC(=NH)NR_{12}R_{13}$, $CH(NH_2)C(=O)OH$, $C(=O)NR_{12}R_{13}$, $C(=O)OR_{12}$, a metal coordination group, a reporter group, a nitrogen-containing heterocycle, a purine, a pyrimidine, a phosphate group, a polyether group, or a polyethylene glycol group,

provided that at least one of said aminodiol monomer subunits in said oligomeric compound does not have structure III;

(g) prior to step (e) or after step (f) contacting said solid support bound aminodiol monomer subunit or said support bound oligomeric compound with a base to remove said base labile amino protecting group to form the solid support bound aminodiol monomer subunit or support bound oligomeric compound having a free amine, and derivatizing said free amine with a group of the formula:

—T—L

wherein:

T is a single bond, a methylene group or a group having formula:

$\{[CR_6R_7]_m\text{-}(R_5)\text{-}[CR_8R_9]_n\text{-}[C(R_{10})]_p\text{-}(E)\text{-}\}_q$

where:

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R_{10} is =O, =S, or =NR₁₁;

R_5 and E, independently, are a single bond, CH=CH, C≡C, O, S, NR₁₁, or C₆-C₁₄ aryl;

each R₆, R₇, R₈, R₉, R₁₁, R₁₂ and R₁₃ are, independently, H, alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, or aryl having 7 to about 14 carbon atoms;

m and n, independently, are 0 to 5;

p is 0 or 1;

q is 1 to about 10;

L is H, substituted or unsubstituted C₂-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, substituted or unsubstituted C₄-C₇ carbocyclic alkyl, substituted or unsubstituted C₄-C₇ carbocyclic alkenyl, substituted or unsubstituted C₄-C₇ carbocyclic alkynyl, substituted or unsubstituted C₆-C₁₄ aryl, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, a nitrogen containing heterocycle, a sulfur containing heterocycle, an oxygen containing heterocycle, a metal coordination group, a conjugate group, halogen, hydroxyl (OH), thiol (SH), keto (C=O), carboxyl (COOH), amide (CONR₁₂), amidine (C(=NH)NR₁₂R₁₃), guanidine (NHC(=NH)NR₁₂R₁₃), glutamyl (R₁₂OOCCH(NR₁₂R₁₃)(CH₂)₂C(=O)), nitrate (ONO₂), nitro (NO₂), nitrile (CN), trifluoromethyl (CF₃), trifluoromethoxy (OCF₃), O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aralkyl, S-aralkyl, NH-aralkyl, amino (NH₂), azido (N₃), hydrazino (NHNH₂), hydroxylamino (ONH₂), sulfoxide (SO), sulfone (SO₂), sulfide (S-), disulfide (S-S), silyl, a nucleosidic base, an amino acid side chain, a carbohydrate, a biopharmaceutically active moiety, or group capable of hydrogen bonding where the substituent groups are

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selected from hydroxyl, amino, alkoxy, alcohol, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, and alkynyl groups;

(h) optionally repeating steps (c) and (d) followed by step (g) to increase the length of the oligomeric compound bound to said solid support;

(i) treating said oligomeric compound bound to said solid support with acid to deprotect any protecting groups; and

(j) cleaving said oligomeric compound from said solid support.

46. (Previously Presented) The process of claim 45 wherein said step (g) is conducted after said step (b).

47. (Previously Presented) The process of claim 45 wherein said step (g) is conducted prior to step (d) for the addition of at least one monomeric subunit to said oligomeric compound.

48. (Previously Presented) The process of claim 45 wherein said step (g) is conducted prior to each iteration of said step (d).

49. (Previously Presented) The process of claim 45 wherein said step (g) is conducted only after at least one iteration of said step (e).

50. (Previously Presented) The process of claim 45 wherein said step (g) is conducted after said step (f) for the addition of at least one monomeric subunit to said oligomeric compound.

51-56. (Cancelled)